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10/088,665	08/14/2002	Keith Alan Foster	18872.0120	5000

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,665	FOSTER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8,9,22-28,31-36 and 38* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,22-28 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 8-9, 22-28, 31-36 and 38 are pending.

2. Applicant's election with traverse of Group I, Claims 1-3, 8-9, 22-25 and 38 (now claims 1-3, 8-9, 22-28 and 38), drawn to a method of inhibiting secretion from a non-neuronal inflammatory cell comprising administering an agent comprising at least first and second domains, wherein the first domain cleaves one or more proteins essential to exocytosis and the second domain translocates the first domain into the inflammatory cell and An agent for inhibiting secretion from a non-neuronal inflammatory cell, comprising at least first, second and third domains, wherein the first domain cleaves one or more proteins essential to exocytosis, the second domain translocates the first domain into the cell and the third domain binds to said non- neuronal inflammatory cell and a pharmaceutical composition comprising said agent that read on the species wherein the third domain is IL-8, filed 1/4/05, is acknowledged. The traversal is on the grounds that the instant National Phase application is based on a PCT application no. PCT/GB00/03681 which was filed on September 25, 2000 which in which claims priority to a United Kingdom application no. G89922558.3 filed on September 23, 1999. These priorities are claimed in the Declaration filed with the application. A request to correct the priority information in the USPTO database and to issue a corrected filing receipt has already been filed.

Upon reconsideration, the product of Group 2 (claims 26-28) has been rejoined with the method of Group 1. Under unity of invention practice as it applies to cases filed under 35 U.S.C. 371, unity of invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

A) A product and a special process of manufacture of said product.

B) A product and a process of use of said product.

C) A product, a special process of manufacture of said product and a process of use of said product.

D) A process and an apparatus specially designed to carry out said process.

E) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and a method of making a product as claimed in the instant application, see MPEP§

1850). Therefore, the requirement of Group 1 (now claims 1-3, 8-9, 22-28 and 38) and Groups 3-4 (now Groups 2-3) is still deemed proper and is therefore made FINAL.

3. Claims 31-36 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 8-9, 22-28 and 38, drawn to a method of inhibiting secretion from a non-neuronal inflammatory cell comprising administering an agent comprising at least first and second domains, wherein the first domain cleaves one or more proteins essential to exocytosis and the second domain translocates the first domain into the inflammatory cell and An agent for inhibiting secretion from a non-neuronal inflammatory cell, comprising at least first, second and third domains, wherein the first domain cleaves one or more proteins essential to exocytosis, the second domain translocates the first domain into the cell and the third domain binds to said non-neuronal inflammatory cell and a pharmaceutical composition comprising said agent that read on the species wherein the third domain is IL-8, are being acted upon in this Office Action.

5. Claims 2-3, 8-9, 22-25 and 27-28 are objected because "A" should have been "The" for said dependent claims.

6. Claim 27 is objected to because said claim depend from canceled claim 4.

7. Claims 8-9 and 38 are objected to for encompassed non-elected embodiments.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 8-9, 22-28 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of inhibiting secretion from a non-neuronal inflammatory cell comprising administering a polypeptide comprising a first domain and a second domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25,

synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell thereby inhibits secretion from said cell, (2) the said method wherein the polypeptide further comprises a third domain wherein the third domain is a ligand capable of binding to the surface of non-neuronal inflammatory cells, (3) a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is a ligand capable of binding to the surface of non-neuronal inflammatory cell and (4) a composition comprising the a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is a ligand capable of binding to the surface of non-neuronal inflammatory cell and a pharmaceutical acceptable carrier, **does not** reasonably provide enablement for a method of inhibiting secretion from any non-neuronal inflammatory cell as set forth in claims 1-3, 8-9, and 22-25 using (1) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (2) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell or for treating any disease, any disease such as the ones recited in claim 9, (3) *any* "agent comprising at least any first and second domains" further comprises any third domain for targeting the agent to said non-neuronal inflammatory cell for the claimed method, (4) a*ny* "agent comprising at least any first and second domains" further comprises any third domain wherein the third domain is IL-8 for the claimed method of inhibiting secretion from any non-neuronal

inflammatory cell, (5) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (6) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the first domain comprises any light chain of a clostridial neurotoxin, any fragment of any light chain of a clostridial neurotoxin, any variant or derivative of any light chain of a clostridial neurotoxin, (7) any "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the second domain comprises any H_N region of a clostridial polypeptide, any fragment of any H_N region of a clostridial polypeptide, any variant or any derivative of any H_N region of a clostridial polypeptide that translocates the exocytosis inhibiting activity of the first domain into the inflammatory cell for the claimed method, (8) any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell, (9) any pharmaceutical composition comprising any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell in combination with a pharmaceutical acceptable carrier and (10) a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal inflammatory cell using any of the agent mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is wheat germ agglutinin capable of binding to the surface of non-neuronal inflammatory cell. The specification further discloses a method of inhibiting secretion of histamine from human umbilical vein endothelial cells in vitro stimulated with von Willebrands factor using the polypeptide mentioned above in the presence low pH (page 42).

The specification does not teach how to make any or all "agent" mentioned above because there is insufficient guidance as to the structure of the "agent" without the amino acid sequence, much less using the undisclosed agent for treating *all* disease such as the ones recited in claims 9 and 38.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). A person of skill in the art could not predict which particular "agents" without the amino acid sequences are essential and could be used in a therapeutic methods encompassed by the claims.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the unlimited number of "agent" and disease, there is a lack of in vivo working example demonstrating that any "agent" is effective for inhibiting secretion from all non-neuronal inflammatory cell, under physiological condition. Let alone treating all disease such as the ones recited in claim 9, including allergies, eosinophilia, asthma, autoimmune disease such as

rheumatoid arthritis, systemic lupus erythematosus, pancreatitis, radiation induced fibrosis, psoriasis, eczema, and other fibrotic disorders.

A method of treating all disease using any agent mentioned above in the absence of in vivo working example is unpredictable for the following reasons: (1) the agent or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the agent or protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-3, 8-9, 22-28 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* or *all* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (2) *all* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting

secretion from any non-neuronal inflammatory cell or for treating any disease, any disease such as the ones recited in claim 9, (3) *any* "agent comprising at least any first and second domains" further comprises any third domain for targeting the agent to said non-neuronal inflammatory cell for the claimed method, (4) a*ny* "agent comprising at least any first and second domains" further comprises any third domain wherein the third domain is IL-8 for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (5) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (6) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the first domain comprises any light chain of a clostridial neurotoxin, any fragment of any light chain of a clostridial neurotoxin, any variant or derivative of any light chain of a clostridial neurotoxin, (7) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the second domain comprises any H_N region of a clostridial polypeptide, any fragment of any H_N region of a clostridial polypeptide, any variant or any derivative of any H_N region of a clostridial polypeptide that translocates the exocytosis inhibiting activity of the first domain into the inflammatory cell for the claimed method, (8) *any* agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell, (9) *any* pharmaceutical composition comprising any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell in combination with a pharmaceutical acceptable carrier and (10) a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal inflammatory cell using *any* "agent" mentioned above without the amino acid sequence.

The specification discloses only a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is wheat germ agglutinin capable of binding to the surface of non-neuronal inflammatory cell. The specification further discloses a method of inhibiting secretion of histamine from human umbilical vein endothelial cells in vitro stimulated with von Willebrands factor using the polypeptide mentioned above in the presence low pH (page 42).

With the exception of the specific polypeptide mentioned above for inhibiting secretion in vitro, there is insufficient written description about the structure associated with function of all agent for inhibiting secretion form all non-neuronal inflammatory cell, much less for treating all disease such as the ones recited in claim 9.

The specification discloses only one polypeptide comprising botulinum neurotoxin BoNT containing endopeptidase activity fused to clostrial toxin heavy chain H_N and WGA, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of agent to describe the genus for the claimed method, the claimed agent and pharmaceutical composition comprising all agent. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-3, 9, 22-24 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/07864 (Feb 26, 1998; PTO 1449).

The WO 98/07864 publication teaches an agent such as a polypeptide comprising a first, second and third domains wherein the first domain is clostridial toxin light chain, fragment and variant or derivatives thereof that cleaves one or more proteins essential to exocytotosis (see page 3, last paragraph, page 6, first paragraph, page 13, in particular), linked to a second domain such as H_N of clostridial toxin heavy chain, fragment, variants and derivatives thereof that translocates the polypeptide into a target cell (see abstract, page 3, last paragraph, page 7, third paragraph, page 13-14, in particular) and a third domain such as Insulin-like growth factor-1 (IGF-1) that targets and binds to a specific cells such as insulin secreting cells (islet cell or endocrine cell), which is non-neuronal cell that involves in pancreatitis or inflammation of the pancreas (see abstract, page 8, first paragraph, in particular). The term "comprising" in claim 1 is open-ended. It expands the claimed agent to include a third domain of the reference polypeptide. The WO 98/07864 publication further teaches a pharmaceutical composition comprising the reference polypeptide and a pharmaceutically acceptable carrier (see claim 39 of WO 98/07864, in particular). The WO 98/07864 publication teaches a method of inhibiting secretion from non-neuronal cell using the reference polypeptide. The reference cleaves one or more vesicle or plasma membrane associated proteins such as SNAP-25, synaptobrevin/VAMP and syntaxin (see page 5, third full paragraph, in particular) that are essential to the specific cellular process of exocytosis and cleavage of these proteins results in inhibition of exocytoxis in non-neuronal cells, eukaryotic cells, insulin secreting cells (see page 4, third paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 3 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07864 (Feb 26, 1998; PTO 1449) in view of WO 96/33273 (Oct 24, 1996; PTO 892) and Van Damme et al (Eur J Immunol 20(9): 2113-8, Sept 1990; PTO 892).

The teachings of the WO 98/07864 publication have been discussed supra.

The invention in claim 8 differs from the teachings of the references only in that the method wherein the third domain is IL8.

The WO 96/33273 publication teaches a method of targeting clostridial toxin to the cell of interest to inhibit secretion from neuronal inflammatory cell comprising administering an agent such as clostridial toxin light chain or fragment thereof that contains the protease activity (see claims 1-3 of WO 96/33273 publication, page 12-13, in particular), a second domain such as H_N of clostridial toxin heavy chain that translocates or internalizes the clostridial toxin light chain into a target cell (see page 13, 1st paragraph, claim 2 of WO 96/33273, in particular) and a targeting moiety (TM) such as inflammatory cytokine such as IL-8 that targets neutrophils (see page 13, 2nd paragraph, Table 1 on pages 24-25, in particular). The WO 96/33273 publication teaches that coupling of clostridial toxin to a new targeting function (the TM) give a novel agent with new biological properties distinct from the native clostridial neural toxin (see page 15, last paragraph, in particular).

Van Damme et al teach IL8 secretion is associated with neutrophil activation during inflammatory reactions (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Insulin-like growth factor-1 (IGF-1) that targets and binds to an insulin secreting cells as taught by WO 98/07864 publication for the IL-8 as taught by the WO 96/33273 publication that binds to the neutrophils as taught by Van Damme et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Van Damme et al teach IL8 secretion is associated with neutrophil activation during inflammatory

reactions (see abstract, in particular). The WO 96/33273 publication teaches that coupling of clostridial toxin to a new targeting function (the TM) give a novel agent with new biological properties distinct from the native clostridial neural toxin (see page 15, last paragraph, in particular). The WO 98/07864 publication teaches cleavage of one or more vesicle or plasma membrane associated proteins such as SNAP-25, synaptobrevin/VAMP and syntaxin by native clostridial neural toxin results in inhibition of secretion or exocytoxis in non-neuronal cells, eukaryotic cells, insulin secreting cells (see page 5, third full paragraph, page 4, third paragraph, in particular).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 4, 2005

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